White Matter Microstructure Associated with Set-shifting and Speed of Information Processing in Healthy Ageing, Mild Cognitive Impairment and Alzheimer's Disease

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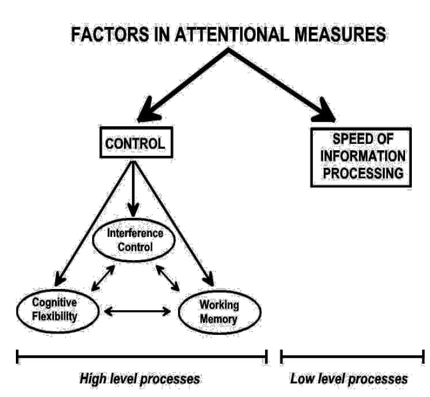
Background

Attentional control and Information processing speed are central concepts in cognitive psychology and neuropsychology. Functional neuroimaging and neuropsychological assessment have depicted theoretical models considering attention as a complex and non-unitary process. One of its component processes, Attentional set-shifting ability, is commonly assessed using the Trail Making Test (TMT). Performance in the TMT decreases with increasing age in adults, Mild Cognitive Impairment (MCI) and Alzheimer's Disease (AD).

Besides, speed of information processing (SIP) seems to modulate attentional performance. While neural correlates of attentional control have been widely studied, there are few evidences about the neural substrates of SIP in these groups of patients. Different authors have suggested that it could be a property of cerebral white matter, thus, deterioration of the white matter tracts that connect brain regions related to set-shifting may underlie the age-related, MCI and AD decrease in performance. The aim of this study was to study the anatomical dissociation of attentional and speed mechanisms.

Diffusion tensor imaging (DTI) provides a unique insight into the cellular integrity of the brain, offering an in vivo view into the microarchitecture of cerebral white matter. At the same time, the study of ageing, characterized by white matter decline, provides the opportunity to study the anatomical substrates speeded or slowed information processing. We hypothesized that FA values would be inversely correlated with time to completion on Parts A and B of the TMT, but not the derived scores B/A and B-A.



Materials and Method

Participants: Four groups of participants (Healthy Young, Healthy aging, MCI and AD) underwent DTI-MRI scans performed on a 3.0T Signa HDx MR scanner (GE Healthcare, Waukesha, WI). Each participant completed the Trail Making Test (TMT) as part of a complete assessment protocol.

	Healthy Young	Healthy Aging	MCI	Alzheimer
N (males)	40 (20)	17 (11)	15 (6)	10 (4)
Mean Age (SD)	28.5 (3.9)	76.1 (7)	75.6(5.3)	76.4(7.8)
MMSE	-	28.4 (2)	24.5 (2.3)	19.9 (4.7)

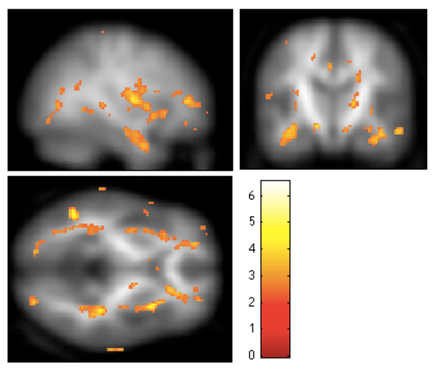
The Trail Making Test (TMT): (Reitan &Wolfson, 1985) is a commonly used measure of executive functioning that assesses cognitive flexibility, selective attention, visual scanning, and visual-motor tracking (Sanchez Cubillo et al., 2007). It is administered in two parts, A and B, both of which require visuomotor tracking. The cognitive flexibility necessary for the set shifting requirement in Part B increases the executive demands of this subtask as evidenced by slower completion times for Part B relative to Part A (Arbuthnott & Frank, 2000). Total time to completion served as the primary dependent variable of task performance. In addition, two derived scores were calculated: TMT B/TMT A (B/A) and TMT-B-TMT-A.

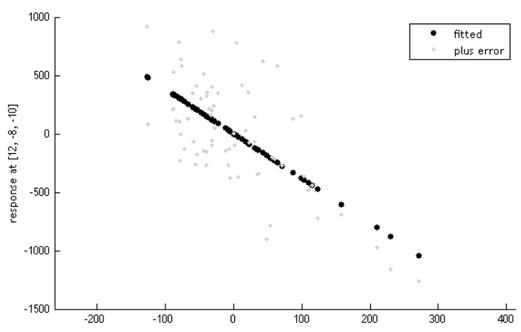
DTI data acquisition: All subjects underwent DTI-MRI scans performed on a 3.0T Signa HDx MR scanner (GE Healthcare, Waukesha, WI). 20 axial slices were obtained along 15 directions with b-value=1000 s/mm2. Matrix=128x128; TE=76; TR=5800; flip angle=90; FOV=24x24; slice thickness=5mm. In addition, a T2 image was acquired (b0). Slices were oriented tin the AC-PC plane.

Image analyses: Fractional anisotropy (FA) values were calculated using DTI-Studio software (Wakana et al., 2004) and analyzed using SPM8 (Wellcome Department of Imaging Neuroscience, London; www.fil.ion.ucl.ac.uk/spm). DTI data were motion and eddy current corrected, spatially normalized to MNI space with an optimized procedure, and smoothed with a 6mm kernel. Correlation between FA and TMT scores for each subject were performed in a voxel-based analysis. Age, brain volume and gender were included as covariates in the analysis. t-maps were overlaid on the average of normalized FA images and presented in neurological convention (R=R). For the labelling of WM tracts the atlas by Mori et al., (2005) and Schmahmann and Pandya (2006) were used.

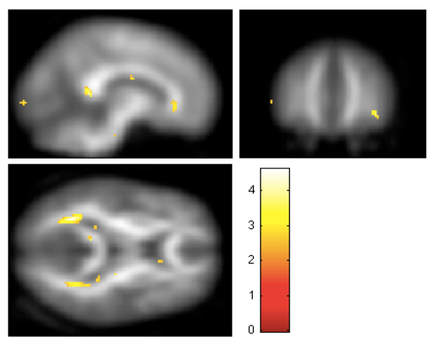
Results

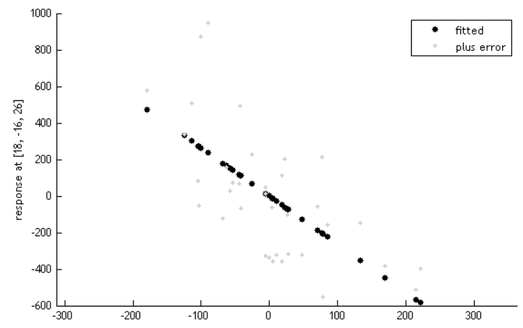
TMT-A



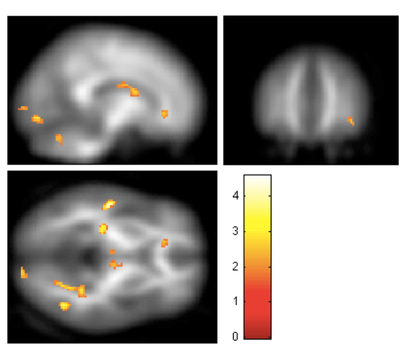


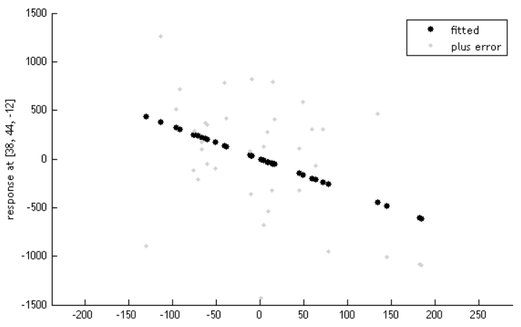
TMT-B



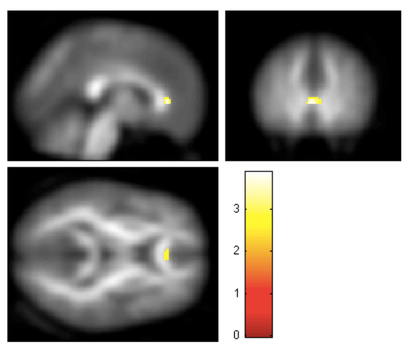


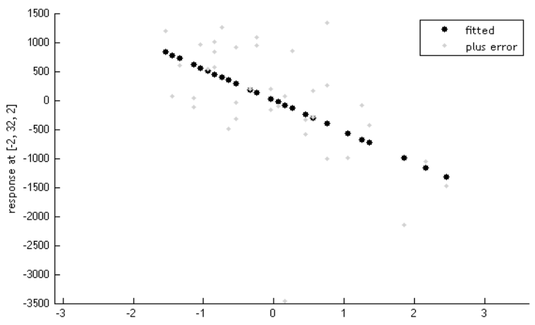
TMT B-A





TMT B/A





Discussion

TMT performance relies on communication among a number of broadly distributed, functionally specialized brain regions. The integrity of the white matter tracts that connect these regions is likely to be a critical factor in TMT performance.

Speed of information and Attentional control seem to be dissociated and may relay on different brain structures. Since set-shifting performance relies on activity in widespread brain regions, deterioration of the white matter tracts that connect these regions may underlie the speed decrease in performance.

Results showed that advancing age, MCI and AD were associated with a progressive decline in speed of information processing and set-shifting performance. A decreased FA in the CC and in multiple association tracts was also found. The analyses showed a correlation between FA and TMT performance where the greater integrity of the cerebral white matter, the better cognitive performance in the speed and set-shifting tests.

DTI analyses revealed a statistically significant correlations between FA and SIP where the greater integrity of the cerebral white matter, the better cognitive performance in the speed tests. However, the load of speed of information is higher in TMT-A than in TMT-B, where set shifting mechanisms are implied. In this view, the widespread distribution of white matter tracts that correlates with TMT-A may reflect the anatomical basis for speed of information processing. As the load of complex attentional mechanisms increase in the task (TMT-B), the influence of white matter decreases.

The two derived scores (B/A, and B-A) are thought to be free of the influence of speed. However, B-A shows a pattern of result highly overlapped with the pattern obtained for TMT-B. In fact this "difference score" may be still reflecting performance time. Some authors have suggested that B/A is a more pure measure of set shifting (Arbuthnot and Frank, 2000; but see Sanchez Cubillo et al., 2000 for a different point of view). Our results show that B/A correlates just with frontal structures, possibly pointing to a more specific measure of frontal lobe function.

DTI results reveal that TMT performance and impairment is partially related to white matter integrity as measured with FA. These initial results suggest that DTI and, particularly FA, is useful for elucidating the neural architecture that underlies specific cognitive functions and deficits.

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Acknowledgements

This study was partially funded by the Spanish Ministry of Science PSI2009-14415-C03-03.

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